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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/12	A1	(11) International Publication Number: WO 97/39746 (43) International Publication Date: 30 October 1997 (30.10.97)
(21) International Application Number: PCT/US97/06464 (22) International Filing Date: 22 April 1997 (22.04.97) (30) Priority Data: 08/636,067 22 April 1996 (22.04.96) US (71) Applicant: ADVANCED POLYMER SYSTEMS, INC. [US/US]; 3696 Haven Avenue, Redwood City, CA 94063 (US). (72) Inventor: ELSON, Melvin, L.; 4081 Highway 96, Burns, TN 37029-5528 (US). (74) Agent: VON MORZE, Herwig; Heller Ehrman White & McAuliffe, Suite 1100, 525 University Avenue, Palo Alto, CA 94301-1900 (US).		(81) Designated States: AU, CN, IL, JP, KR, NZ, SG, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: METHOD OF AND COMPOSITION FOR TREATING DISORDERS OF THE SKIN USING VITAMIN K (57) Abstract A method of treatment of blood disorders of the skin and other conditions of the skin which include, but are not limited to, rosacea, spider veins and inflammatory conditions of the skin by the topical application of a vitamin K composition is described. The composition comprises a vitamin K composition mixture which includes a number of the following substances: natural and synthetic vitamin K, 95 % ethyl alcohol SD40, isopropyl alcohol 99 %, benzyl alcohol, lecithin granules, isopropyl palmitate NF, propyl paraben, methyl paraben, Pluronic F-127 NF, Dowicil 200 and preserved water. The concentrations of the substituent compounds vary in the different formulations of the vitamin K composition.		

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DESCRIPTION

METHOD OF AND COMPOSITION FOR TREATING DISORDERS OF THE SKIN USING VITAMIN K

5 TECHNICAL FIELD

The present invention relates generally to a method of and composition for treating disorders of the skin and more particularly to a method of treating blood vessel disorders of the skin and other conditions of the skin which include, but are not limited to, rosacea, spider veins and inflammatory conditions of the skin by the topical application of a vitamin K composition.

BACKGROUND ART

Human skin undergoes a great deal of changes as it ages-both intrinsic and extrinsic. Part of these changes occur in the vascular system. Aged dermis is relatively avascular. There is an absolute loss of vertical capillary loops in the papillary dermis as well as a decrease in the number of veil cells (fibroblast like cells that deposit basement membrane materials around vessels in response to vascular insults). In addition to these intrinsic changes, photo aging also affects the vasculature of the skin in that changes in the collagen supporting the vessels create an environment in which the vessels break, become dead end vessels, decrease in size and become fragile. The least bit of trauma induces either purpura or an erosion of the surface.

Treatment of vascular problems of the skin and subcutaneous tissue is a major area of dermatological therapy given the increasingly large aging population. A number of dermatological conditions which involve blood vessel disorders of the skin and skin disorders caused by photoaging include actinic and iatrogenic purpura, lentigines, telangiectasia of the face, spider angiomas, spider veins of the face, spider veins of the legs as well as other

vascular problems of the skin and subcutaneous tissue. There is currently no treatment for actinic or iatrogenic purpura. Thus, treatments for these various blood vessel disorders of the skin are clearly limited at best.

5 Rosacea is a common disorder of the skin of the face that is characterized by redness, increased blood vessel flow, increased blood vessels, and the consequences thereof being primarily papular and pustular formations from oil glands, particularly of the nose. The inciting factor is increased blood flow to the central portion of the face
10 and subsequent events occur because of this increased blood flow.

 Current treatment of rosacea consists of use of systemic or topical antibiotics as well as cleansers to decrease the oil gland activity, cortisone preparations to decrease the redness, and
15 metronidazole cream or gel. The use of antibiotics and metronidazole are quite successful in alleviating most of the papular portion of the disease process; however, the redness remains a difficult problem and is very disconcerting to patients. Only systemic or topical steroids
20 have been used with any degree of success to treat the associated redness. Both of these have significant side effects, such as systemic steroids with known side effects of inducing iatrogenic Cushing's
 disease. Topical steroids when used over a great period of time, including hydrocortisone on the face, can produce atrophy of the skin, acne, folliculitis, and telangiectasia.

 Spider veins of the face, particularly in females, is a common
25 problem thought to be due to a number of interacting factors including inheritance, estrogen therapy, trauma, and photodamage. Currently, treatment consists of electrodesiccation, laser therapy, or camouflage makeup. The problems with the current therapy include
 that electrodesiccation is painful, may scar, and the vessels recur
30 more than 50% of the time and have to be retreated. Laser therapy is expensive, painful, and can scar significantly before final resolution is obtained.

Anti-inflammatory topical agents currently available include fluorinated topical steroids, hydrocortisone, and derivatives thereof both over the counter and by prescription. The side effects of these agents are well known and include atrophy, folliculitis, acne, and
5 astrea.

Vitamin K is necessary for the production via the liver of active prothrombin (Factor II), proconvertin (Factor VII), plasma thromboplastin component (Factor IX) and Stuart Factor X. Vitamin K is found in the form of vitamin K-1 (produced by green leafy
10 vegetables) and vitamin K-2 (produced by gastrointestinal bacteria). In addition, vitamin K analogs have been synthesized and currently include vitamins K-3, K-4, K-5, K-6 and K-7. Naturally occurring in many foods, especially green leafy vegetables, the minimum daily requirement for vitamin K-1 has not been established. Most data
15 accumulated regarding hypovitaminosis K is in the newborn. Guillamoont, Sann et al reported in the Journal of Pediatric Gastroenterology and Nutrition that hepatic phylloquinone storage at birth was poor (< 1 microgram) and that the newborn infant might be in a situation of potential deficiency and prophylactic
20 administration of the vitamin would be essential in neonatal surgical situations to prevent excessive bleeding. This deficiency in the new born period is due to two factors--the only sources are green leafy vegetables (for vitamin K1) and synthesis (of vitamin K2) by gastrointestinal bacteria, which are not yet established in the
25 newborn.

Phytonadione (Vitamin K1; 2-methyl-3-phytyl-1-4-naphthoquinone) is a vitamin, which is clear yellow, viscous and odorless. It is insoluble in water and slightly soluble in alcohol. Its empirical formula is $C_{31}H_{46}O_2$ and its structural formula is

30 Clinical uses of Vitamin K in the past have been directly linked with its ability to influence coagulation rather than any deficiency disease process, primarily in anticoagulant-induced

prothrombin deficiency caused by coumarin or indanedione derivatives, hypoprothrombinemia due to antibacterial therapy, factors limiting absorption, or salicylism.

5 The use of vitamin K parenterally has been standard therapy in surgery and internal medicine for many decades. It has also been indicated in the past that the ingestion of foods high in vitamin K content could decrease excessive menstrual flow and influence other bleeding diatheses.

10 Although the use of topical tretinoin and the alpha hydroxy acids may significantly improve photoaged skin in terms of both color and texture and studies have shown a re-establishment of some of the vasculature after tretinoin, no treatment has been effective in the alleviation of actinic purpura.

15 In addition, there are a number of clinical situations in which there is increased bleeding diathesis into the skin, such as steroidal therapy--both systemic and topical as well as salicylates, and many disease states. These situations can be very disconcerting to the patient.

20 What is needed, then, is a method of treating blood vessel disorders of the skin and other skin conditions that is effective and yet is less traumatic to the patient. Such a method is lacking in the prior art.

DISCLOSURE OF THE INVENTION

25 The present invention relates to a composition and method of treating blood vessel disorders of the skin using vitamin K. I have discovered that disorders of the skin which respond to treatment by use of vitamin K include but are not limited to actinic and iatrogenic purpura, lentigines, telangiectasias of the face, spider angiomas,
30 spider veins of the face, spider veins of the legs and other vascular problems of the skin and subcutaneous tissue. Additionally, rosacea and inflammatory conditions of the skin, such as contact dermatitis,

also respond to treatment with vitamin K.

With the foregoing summary of my invention in mind, it is an object of this invention to provide a method of treatment of various blood vessel disorders of the skin using vitamin K in addition to providing a formula for a vitamin K cream to treat various blood vessel disorders of the skin.

It is an additional object of this invention to provide a method for treatment of rosacea , spider viens and inflammatory skin conditions such as contact dermatitis using vitamin K, as well as a formula for a vitamin K cream to treat rosacea , spider viens and inflammatory skin conditions such as contact dermatitis.

It is a further object of this invention that the method developed in this application will enable topical vitamin K treatment of superficial vascular disorders of the skin. One noteworthy advantage of the present use of a vitamin K cream formulation is the ease of treatment. Currently, laser surgery is the primary method of treatment for spider veins. Surgery is clearly a less desirable procedure than topical application of a cream. Not only does the application of a cream provide an easier and less traumatic method of treatment, it will also reduce the cost involved in treating this medical problem.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention provides a method of treatment of vascular disorders of the skin by using a vitamin K cream and a formula for the composition of the cream itself. The present invention comprises the use of vitamin K in the form of either vitamin K-1 (Phytonadione) or vitamin K-2 in a topical formulation for the treatment of actinic and iatrogenic purpura among other disorders of the skin. The use of a topical vitamin K-1 containing cream is effective in the treatment of actinic and iatrogenic purpura and lentigines, among other disorders of the skin.

My composition containing 1% vitamin K-1 in a unique cream base system delivers vitamin K into the skin and appears to have an influence on the disappearance of extravascular blood, as well as decreasing the incidence of purpura, when compared to its base, when used on a twice daily basis. No benefit was obtained on the appearance of intact vessels of the skin when comparing the active to the placebo agent. There appears to be no effect on the vessel themselves, only on leaking vessels and blood already outside the dermal vascular system with this particular formulation and concentration.

VITAMIN K-1 CREAM-5%

A preferred embodiment of the cream of the present invention comprises the compounding formula of a vitamin K-1 cream-5%. To mix a 100 gram quantity of the vitamin K-1 5% cream, it is necessary to mix 5 grams of Phytonadione (Roche Vitamine & Fine Chemicals, Hoffman-LaRoche Inc., Belvidere, N.J.), 5 ml of 95% ethyl alcohol SD40, 2 ml of benzyl alcohol (Carrubba, Inc., Milford, Ct.), 10 grams of lecithin granules (American Lecithin Co., Danbury, Ct.), 10 ml of isopropyl palmitate NF (Amerchol corp., Edison, N.J.), and 20 grams Pluronic F-127, NF (BASF corp., Parsippany, N.J.). The mixture is then QS'ed to 100 grams with preserved water. In the above preferred embodiment, Pluronic F-127, NF is a known surfactant.

VITAMIN K-1 CREAM-1%

A preferred embodiment of the cream of the present invention comprises the compounding formula of a vitamin K-1 cream-1%. To mix a 100 gram quantity of the vitamin K-1 cream-1%, it is necessary to mix 1 gram of Phytonadione (Roche Vitamine & Fine Chemical, Hoffman-LaRoche Inc., Belvidere, N.J.), 2.42. ml of 99% isopropyl alcohol (Ruger Chemical Co., Irvington, N.J.), 1.73 ml of benzyl alcohol (Carrubba, Inc., Milford, Ct.), 8.26 grams of lecithin granules (American Lecithin Co., Danbury, Ct.), 7.44 ml of isopropyl palmitate

NF (Amerchol Corp., Edison, N.J.), and 16.53 grams Pluronic F-127, JF (BASF Corp., Parsippany, N.J.), 0.04 gram propyl paraben (Ruger Chemical Corp., Irvington, N.J.), 0.13 gram methyl paraben (Ruger Chemical Corp., Irvington, N.J.), 0.04 gram Dowicil 200 (Ruger Chemical Corp., Irvington, N.J.) and 62.41 ml distilled water. In the above preferred embodiment, Pluronic F-127, NF is a known surfactant.

EXAMPLE 1 - CASE STUDY - TREATMENT WITH VITAMIN K-1 CREAM (0.8% TO 1%)

The initial study of the effects of a vitamin K-1 cream used in treatment of blood vessel disorders of the skin and skin disorders caused by photoaging involved use of a cream of 0.8% to 1% concentration of vitamin K-1 in June, 1993 on actinic and iatrogenic purpura among other skin disorders. Twelve patients were selected to apply this medication twice daily and all noticeably benefited from its use.

The twelve patients who were chosen to participate in the study had purpura on the hands and arms. Patients for easy bruising were solicited by newspaper as well as from hematologists and rheumatologists. Two creams were prepared, one with vitamin K-1 (0.8% to 1%) and one identical except with no vitamin K and added yellow color to make the agents appear the same. Because of the size of the vitamin K molecule, it was necessary to develop a unique delivery system to ensure penetration.

At the commencement of this study, patients were evaluated and photographed. Informed consent was obtained from the patients. Patients were instructed according to the following protocol:

1. Apply Cream A to the back of the right hand and the lower arm with the left hand using an amount the size of a pea.
2. Apply Cream B to the back of the left hand and the lower arm with the right hand using an amount the size

of a pea.

3. Use no moisturizers, no glycolic acid, no Retin A and no topical medications on the hands during the period of this study.
4. Return in 2,4 and 6 weeks for evaluation and further photographs.

The additional 6 patients were entered into a separate protocol to determine the possibility of the topical agent decreasing the appearance of spider veins of the face according to the following protocol:

1. Apply Cream A with the right hand to the right side of the face and Cream B to the left side of the face with the left hand at bedtime on dry skin.
2. Wash hands immediately after application.
3. Use no Retin A, glycolic acid or moisturizers during the study.
4. Return in 2,4 and 6 weeks for photographs.

Within 4 weeks of application, all patients with actinic purpura and easy bruising had a decrease in the time required for healing on the active compound side compared to the opposite (placebo) side as well as a decreased appearance of lesions following trauma. No patients reported adverse effects of the active cream or the placebo--no itching, erythema, dryness, etc. Two patients noticed a decrease in the lentigines on the active side versus the placebo side, which was also evident in photographs.

EXAMPLE 2 - CASE STUDY - TREATMENT WITH VITAMIN K-1 CREAM-5%

A case study of the effects of a vitamin K-1 cream-5% used in treatment of blood vessel disorders of the skin and skin disorders caused by photoaging involve the use of a vitamin K-1 cream having a 5% concentration of vitamin K-1 on five patients. The patients

exhibited blood vessel disorders on certain areas of the body. The disorders had been caused by either trauma, surgery or sun damage.

Two creams were prepared, one with vitamin K-1 (5%) and one identical except with no vitamin K and added yellow color to make the agents appear the same. Because of the size of the vitamin K molecule, it was necessary to develop a unique delivery system to ensure penetration.

At the commencement of this study, patients were evaluated and photographed. Informed consent was obtained from the patients.

Patients were instructed according to the following protocol:

1. Apply Cream A with the right hand to the right side of the face and Cream B to the left side of the face with the left hand at bedtime on dry skin.
2. Wash hands immediately after application.
3. Use no Retin A, glycolic acid or moisturizers during the study.
4. Return in 2,4 and 6 weeks for photographs.

Three out of the five patients showed a decrease in the appearance of true blood vessels following application of the vitamin K-1 cream-5%.

EXAMPLE 3 - METHOD OF TREATING ROSACEA USING VITAMIN K CREAM

Fifty consecutive patients with rosacea were treated in the usual manner including antibiotics (primarily tetracycline and metronidazole gel) with the addition of 1% phytonadione cream twice daily. After two weeks, greater than 75% of the patients noted a decrease in the redness, and after six weeks, virtual clearing of the redness for the most part in these patients was observed. They were also capable of decreasing the use of the metronidazole and the systemic antibiotics to the point that greater than 20% were able to continue with treatment utilizing only the Vitamin K topically to

continue to remain clear.

EXAMPLE 4 - METHOD OF TREATING SPIDER VEINS USING VITAMIN K CREAM

5 Patients undergoing electrodesiccation of their vessels were treated with 1% phytonadione cream following electrodesiccation of the blood vessels to prevent recurrence and to increase healing. Ninety percent of the patients had complete resolution after one treatment using the 1% phytonadione cream. Additionally, 20
10 patients used only the cream without prior electrodesiccation and after four months noticed improvement of the appearance of the vessels. The use of the Vitamin K cream is effective in treatment of spider veins of the face in greater than 75% of cases and certainly decreases the recurrence rate.

15

EXAMPLE 5 - ANTI- INFLAMMATORY ACTIVITY OF VITAMIN K CREAM

 A protocol was instituted using 1% phytonadione cream at the following chemical peeling with glycolic acid 70%. Three thousand
20 two hundred (3,200) consecutive treatments were performed utilizing 1% phytonadione cream afterwards and this significantly decreased the discomfort in virtually all patients. All but three patients had resolution of the erythema, two patients had persistent erythema for the next two days, and one went on to develop vesicles and crusts.
25 This compares more than favorable with hydrocortisone in the past as well as cartilage preparation creams. Alleviation of the discomfort following cosmetic procedures, particularly chemical peeling, have a tremendous advantage for both patient and physician as this decreases morbidity significantly. Additionally, a number of
30 patients have used 1% phytonadione for the treatment of acute contact dermatitis. Twenty (20) patients were chosen to apply this medication four times daily upon the development of contact

dermatitis due to poison ivy or some other source. Patients received immediate relief from applying the medication and healing was much more rapid than with no treatment at all.

5

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While there have been described particular embodiments of the present invention of a new and useful formulation of and method of using a vitamin K cream in topical therapy for the treatment of disorders of the skin, it is not intended that such references be construed as limitations upon the scope of this invention except as set for the in the following claims. Further, although there have been described certain quantities and proportions used in the formulation of the preferred embodiments, it is not intended that such quantities and proportions be construed as limitations upon the scope of this invention except as set further in the following claims.

CLAIMS

What I claim is:

1. A method of treating rosacea comprising:
 - a) formulating a pharmaceutical composition comprising a
5 vitamin K cream ranging in concentration from a 0.01%
vitamin K composition to a 50% vitamin K composition;
 - b) applying said pharmaceutical composition topically to
affected areas.
2. The method according to claim 1 wherein the vitamin K
10 pharmaceutical composition is applied to affected areas twice daily.
3. The method according to claim 1 wherein the form of
vitamin K used in said pharmaceutical composition is selected from
the group consisting of vitamin K-1, vitamin K-2 and synthetic
vitamin K analogs.
- 15 4. A method of treating rosacea as in claim 1, wherein the
method comprises:
 - a) formulating a pharmaceutical composition comprising a
form of vitamin K in combination with a plurality of
substituents from the group comprising: 95% ethyl
20 alcohol, isopropyl alcohol 99%, benzyl alcohol, isopropyl
palmitate, lecithin soya granular, Pluronic F-127 NF,
methyl paraben, propyl paraben, Dowicil 200, and
water; and
 - b) applying said pharmaceutical composition topically to
25 affected areas.
5. The method of treating rosacea according to claim 4
wherein a vitamin K-1 cream 5% composition comprising 5 grams of
vitamin K-1 (Phytonadione), 5 ml 95% ethyl alcohol SD40, 2 ml
benzyl alcohol, 10 grams lecithin granules, 10 ml isopropyl palmitate
30 NF, 20 grams Pluronic F-127 NF, and preserved water to QS said
composition to 100 grams is applied topically to affected areas.

6. A method of treating rosacea according to claim 4, wherein a vitamin K-1 cream 1% composition, comprising 1 gram vitamin K-1 (Phytonadione), 2.42 ml of 99% isopropyl alcohol, 1.73 ml of benzyl alcohol, 8.26 grams of lecithin granules, 7.44 ml of isopropyl palmitate NF, and 16.53 grams Pluronic F-127, NF, 0.04 gram propyl paraben, 0.13 gram methyl paraben, 0.04 gram Dowicil 200 and 62.41 ml distilled water, is applied topically to affected areas.

7. A method of treating spider veins comprising:

- a) formulating a pharmaceutical composition comprising a vitamin K cream ranging in concentration from a 0.01% vitamin K composition to a 50% vitamin K composition;
- b) applying said pharmaceutical composition topically to affected areas.

8. The method according to claim 7 wherein the vitamin K pharmaceutical composition is applied to affected areas twice daily.

9. The method according to claim 7 wherein the form of vitamin K used in said pharmaceutical composition is selected from the group consisting of vitamin K-1, vitamin K-2 and synthetic vitamin K analogs.

10. A method of treating spider veins according to claim 7 wherein the method comprises:

- a) formulating a pharmaceutical composition comprising a form of vitamin K in combination with a plurality of substituents from the group comprising: 95% ethyl alcohol, isopropyl alcohol 99%, benzyl alcohol, isopropyl palmitate, lecithin soya granular, Pluronic F-127 NF, methyl paraben, propyl paraben, Dowicil 200, and water; and
- b) applying said pharmaceutical composition topically to affected areas.

11. The method of treating spider veins according to claim 10 wherein a vitamin K-1 cream 5% composition comprising 5 grams

of vitamin K-1 (Phytonadione), 5 ml 95% ethyl alcohol SD40, 2 ml benzyl alcohol, 10 grams lecithin granules, 10 ml isopropyl palmitate NF, 20 grams Pluronic F-127 NF, and preserved water to QS said composition to 100 grams is applied topically to affected areas.

5 12. A method of spider veins according to claim 10 wherein a vitamin K-1 cream 1% composition, comprising 1 gram vitamin K-1 (Phytonadione), 2.42 ml of 99% isopropyl alcohol, 1.73 ml of benzyl alcohol, 8.26 grams of lecithin granules, 7.44 ml of isopropyl palmitate NF, and 16.53 grams Pluronic F-127, NF, 0.04 gram propyl
10 paraben, 0.13 gram methyl paraben, 0.04 gram Dowicil 200 and 62.41 ml distilled water, is applied topically to affected areas.

13. A method of treating inflammatory conditions of the skin comprising:

- 15 a) formulating a pharmaceutical composition comprising a vitamin K cream ranging in concentration from a 0.01% vitamin K composition to a 50% vitamin K composition;
- b) applying said pharmaceutical composition topically to affected areas.

14. The method according to claim 13 wherein the vitamin
20 K pharmaceutical composition is applied to affected areas four times daily.

15. The method according to claim 13 wherein the form of vitamin K used in said pharmaceutical composition is selected from the group consisting of vitamin K-1, vitamin K-2 and synthetic
25 vitamin K analogs.

16. The method according to claim 13 wherein the inflammatory condition of the skin comprises contact dermatitis.

17. A method of treating inflammatory conditions of the skin according to claim 13 wherein the method comprises:

- 30 a) formulating a pharmaceutical composition comprising a form of vitamin K in combination with a plurality of substituents from the group comprising: 95% ethyl alcohol, isopropyl alcohol 99%,

benzyl alcohol, isopropyl palmitate, lecithin soya granular, Pluronic F-127 NF, methyl paraben, propyl paraben, Dowicil 200, and water; and

5 b) applying said pharmaceutical composition topically to affected areas.

18. The method of treating inflammatory conditions of the skin according to claim 17 wherein a vitamin K-1 cream 5% composition comprising 5 grams of vitamin K-1 (Phytonadione), 5 ml 95% ethyl alcohol SD40, 2 ml benzyl alcohol, 10 grams lecithin granules, 10 ml isopropyl palmitate NF, 20 grams Pluronic F-127 NF, and preserved water to QS said composition to 100 grams is applied topically to affected areas.

19. A method of inflammatory conditions of the skin according to claim 17 wherein a vitamin K-1 cream 1% composition, comprising 1 gram vitamin K-1 (Phytonadione), 2.42 ml of 99% isopropyl alcohol, 1.73 ml of benzyl alcohol, 8.26 grams of lecithin granules, 7.44 ml of isopropyl palmitate NF, and 16.53 grams Pluronic F-127, NF, 0.04 gram propyl paraben, 0.13 gram methyl paraben, 0.04 gram Dowicil 200 and 62.41 ml distilled water, is applied topically to affected areas.

20. A pharmaceutical composition for topical application to treat skin disorders, said composition including vitamin K ranging in concentration from 0.01% to 50%, the balance of the composition including a mixture of carrying agents, alcohol and water, the balance of the composition functioning to deliver the vitamin K into the skin.

21. The pharmaceutical composition as in claim 20 wherein the vitamin K in the pharmaceutical composition is selected from the group consisting of vitamin K-1, vitamin K-2 and synthetic vitamin K analogs.

22. The pharmaceutical composition as claimed in claim 20, wherein the concentration of Vitamin K in the pharmaceutical

composition is about 5% by weight.

23. The pharmaceutical composition as claimed in claim 22, wherein the balance of the composition includes substantially 5 ml ethyl alcohol, substantially 2 ml benzyl alcohol, substantially 10
5 grams lecithin granules, substantially 10 ml isopropyl palmitate NF, substantially 20 grams Pluronic F-127 NF, and preserved water to QS said composition to substantially 100 grams.

24. The pharmaceutical composition as claimed in claim 20, wherein the concentration of Vitamin K in the pharmaceutical
10 composition is about 1% by weight.

25. The pharmaceutical composition as in claim 24, wherein the balance of the composition includes substantially 2.42 ml of 99% isopropyl alcohol, substantially 1.73 ml of benzyl alcohol, substantially 8.26 grams of lecithin granules, substantially 7.44 ml of
15 isopropyl palmitate NF, substantially 16.53 grams Pluronic F-127, NF, substantially 0.04 gram propyl paraben, substantially 0.13 gram methyl paraben, substantially 0.04 gram Dowicil 200 and substantially 62.41 ml distilled water.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/06464

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/12

US CL :514/681

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/681

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, --P Y,	US 5,510,391 A (ELSON) 23 April 1996, see the abstract and column 3, line 19 - column 4, line 6.	10-12 and 20-25 ----- 1-9
Y	US 5,162,377 A (KAKOKI et al.) 10 November 1992, see column 2, lines 37-61, column 3, line 40, column 4, line 5 and Examples 9, 10, 13 and 14.	20-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

06 AUGUST 1997

Date of mailing of the international search report

29 AUG 1997

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